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Anti-Tumour Treatment

What to choose as radical local treatment for lung metastases from colo-rectal cancer: Surgery or radiofrequency ablation?

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SUMMARY

Background: Long-term survival can be obtained with local treatment of lung metastases from colorectal cancer. However, it is unclear as to what the optimal local therapy is: surgery, radiofrequency ablation (RFA) or stereotactic radiotherapy (SBRT).
Methods: A systematic review included 27 studies matching with the a priori selection criteria, the most important being ⩾50 patients and a follow-up period of ⩾24 months. No SBRT studies were eligible. The review was therefore conducted on 4 RFA and 23 surgical series.
Results: Four of the surgical studies were prospective, all others were retrospective. No randomized trial was found. The reporting of data differed between the studies, which led to difficulties in the analyses. Treatment-related mortality rates for RFA and surgery were 0% and 1.4–2.4%, respectively, whereas morbidity rates were reported inconsistently but seemed the lowest for surgery.
Conclusion: Due to the lack of phase III trials, no firm conclusions can be drawn, although most evidence supports surgery as the most effective treatment option. High-quality trials comparing currently used treatment modalities such as SBRT, RFA and surgery are needed to inform treatment decisions.

Introduction

Colorectal cancer is the third most common tumor type in males, and the second in females, with in 2008 an incidence of 1.2 million new cases and a mortality rate of over 600.000 world-wide.[1] In the Netherlands, approximately 20% of colorectal cancer patients have synchronic metastatic disease at time of diagnosis.[2]

Although the cure rate of patients with colorectal cancer has improved over the last decades, distant metastases are still of concern. Temporary remissions with systemic treatment can be obtained, but most of the time, cure remains elusive once distant metastases have occurred. In 1995, Hellman and colleagues proposed an intermediate state between localized cancer and distant metastases, called "oligo-metastases".[3] In this concept, treatment of a few distant metastases with curative intent may still be possible, if all visible cancer can be eradicated with local treatments such as radiotherapy, surgery or radiofrequency ablation (RFA).

The observation that long-term survival may be achieved with surgical resection of liver metastases from colorectal cancer[4] has been used as an argument supporting the oligo-metastases concept. Besides liver, also lung metastases from colorectal cancer have been treated with curative or radical intent. Most series deal with surgery, although RFA and Stereotactic Body Radiation Therapy or SBRT[5] (also called SABR, Stereotactic Ablative RadioTherapy) are used as well. Most studies included patients with several types of primary tumors, whilst few studies reported outcomes on lung metastases from primary colorectal cancer, only. To the best of our knowledge, most series are retrospective or observational

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and no randomized series investigating survival outcome of these treatment modalities have been published. This was the reason for Treasure et al.[6] to perform an ongoing phase III trial that investigates whether or not pulmonary metastasectomy in colorectal cancer influences survival.

Several systematic reviews regarding one or more of the three local treatment methods have been published.[7–9] However, to the best of our knowledge, no systematic review has been reported comparing the outcome of surgery, RFA and SBRT specifically in the treatment of lung metastases of colorectal cancer. This was the aim of the current review.

Methods

Search strategy and selection criteria

The literature search was performed by using a broad strategy which was composed by following the PICO method[10,11] (Supplementary Material 1). The complete search strategy is shown in Appendix 1 and was used to identify studies in Pub Med, EMBASE, Web of Science and the Cochrane Library from 2001 until the search date in October 2011.

For this review a priori selection criteria were established prior to the search and selection of articles. These included a minimal follow-up period of 24 months, a minimum of 50 patients included in the study with pulmonary metastases from colorectal cancer without constraint on previous therapies. Only original articles were included. Another limitation used was language, in which only English, German and Dutch articles were included. All inclusion- and exclusion criteria are summarized in Table 1.

In order to complete the search and to identify all relevant studies, the references of all eligible articles were manually searched for other potentially relevant studies.

Outcomes

One researcher conducted the search and selection of eligible studies. All articles were then evaluated by two independent reviewers. When available, the following data were obtained from the trials: patient and tumor characteristics, inclusion- and exclusion criteria, disease-free interval, treatment technique, follow-up, complications, tumor progression, recurrence rate, survival and prognostic factors.

One researcher (R.S.) reviewed all eligible studies, whereas the second extraction was performed by three reviewers (R.H., J.G. and D.D.R.). Data were extracted and tabulated independently in order to reach validity of the data (appendix 2 for extraction table). If outcomes differed, there was discussion between the reviewers until consensus was reached.

Results

Search results

The initial search in the four databases included 4727 articles in total, which were searched for duplicates using Endnote by which 453 duplicates were excluded.

Table 1
Inclusion and exclusion criteria for the literature search.

Follow-up period	⩾24 months
Site of primary tumor	Colorectal carcinoma
Number of patients	⩾n = 50
Previous treatment	All therapies
Tumor stage	Stage IV
Type of metastasis	Recurrence or first secondary tumor
Study type	Reviews excluded

The remaining studies were manually evaluated and 226 more duplicates were excluded. Another 3250 studies were then excluded based on titles that were not relevant for this study (Fig. 1) leaving a total of 798 studies for further analysis.

Abstracts of all remaining 798 studies were then compared to the a priori selection criteria. Studies not matching these criteria were excluded as well. After this first selection, 27 relevant studies were identified and included in this review. Of these 27, the majority (23) focused on surgery, four examined RFA and none regarded SBRT.

Description of the studies

Of the twenty-seven studies that matched the selection criteria and were included in this review, four studies investigated RFA, all of which were retrospective.[12–15] Three of these studies were performed in the same institute in Sydney, Australia[13–15] with two of these papers[13,14] investigating the same patient population. In our analysis, we used this population only once. All twenty-three remaining studies reviewed surgical metastasectomy, of which four prospective studies and the remaining retrospective studies. Study and patient characteristics are found in Table 2.

Despite the known importance according to the "oligo-metastases hypothesis",[3] only six studies reported on the median or mean number of the pulmonary lesions. Yan et al.[13,14] reported a median of 2 lesions per patient (range, 1–6), whilst Kanemitsu et al.[16] and Pfannschmidt et al.[17] found a median of 1 lesion per patient (ranges, 1–8 and 1–35 lesions, respectively). Two series only reported mean values of 2.3 ± 2.1 lesions[18] and 1.6 ± 0.8 lesions.[19]

Other study and patient characteristics such as tumor diameter and follow-up durations are listed in Table 2.

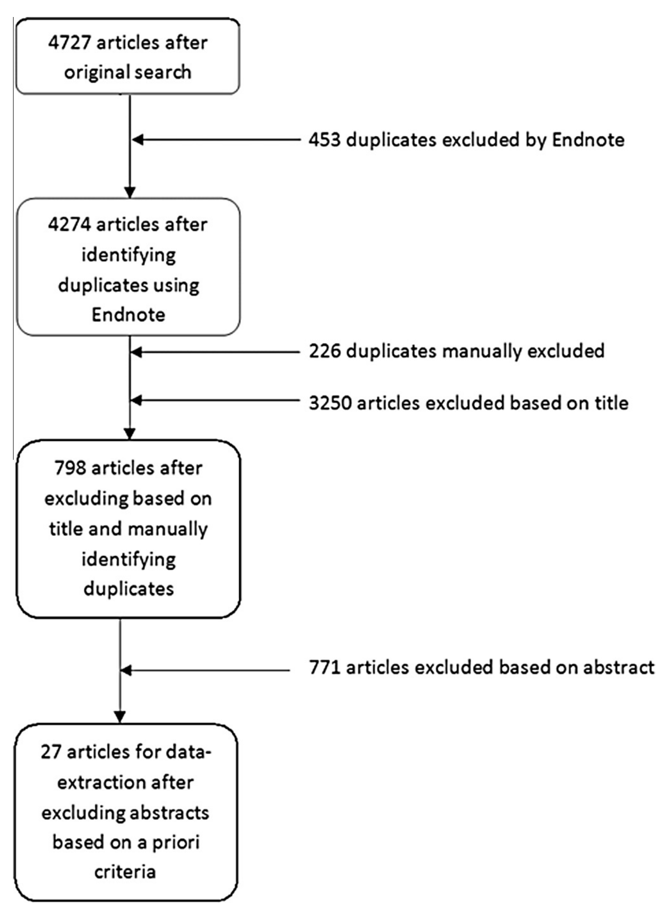

Fig. 1. Flowchart of selection process.

Table 2
Patient characteristics.

Study	Patient sex/age	No. of tumors	Involved lobes	Tumor diameter	Follow-up
Yamakado (2009); RFA, CT guided; (Retrospective, $n = 78$); Mie, Japan	Sex: M/F: 53/25; mean age 66.1 ± 9.8y (range, 40–87 year); ⩽65 year: $n = 29$; >65 year: $n = 49$	1 lesion: $n = 34$; ⩾2 lesions: $n = 44$	Unilateral $n = 49$; Bilateral $n = 29$	Mean max size: 2.0 ± 1.0 cm (range 0.6–6.0 cm); TD ⩽ 3 cm $n = 70$; TD > 3 cm $n = 8$	Mean 24.6 months ± 17.6 months (range, 6.0–84.1 months)
Yan (2006); RFA, CT guided; (Retrospective, $n = 55$); Sydney, Australia	Sex: M/F: 33/22; mean age 62 ± 11 year; ⩽65 year: $n = 29$; >65 year: n = 26	1–2 lesions: $n = 39$; 3–6 lesions: $n = 16$; mean pp 2 lesions ± 2; median pp 2 lesions (range, 1–6)	1 lobe: $n = 39$, 2–4 lobes $n = 16$	Mean max size: 2.1 ± 1.1 cm; TD ⩽ 3 $n = 42$; TD > 3 cm $n = 13$	Median 24 months (range, 6–40 months): complete FU
Yan (2007); RFA, CT guided; (Retrospective, $n = 55$); Sydney, Australia	Sex: M/F: 33/22; mean age 62 ± 11 year; ⩽65 year: $n = 29$; >65 year: $n = 26$	1–2 lesions: $n = 39$; 3–6 lesions: $n = 16$; mean pp 2 lesions ± 2; median pp 2 lesions (range, 1–6)	1 lobe: $n = 39$, 2–4 lobes $n = 16$	Mean max size: 2.1 ± 1.1 cm; TD ⩽ 3 $n = 42$; TD > 3 cm $n = 13$	Median 24 months (range, 6–40 months): complete FU
Chua (2010); RFA, CT guided; (Retrospective, $n = 108$); Sydney, Australia	Sex: M/F: 83/65; median age 63 year (range 30–85); ⩽60 year: $n = 50$; >60 year: $n = 98$	1–2 lesions: $n = 104$; ⩾3 lesions: $n = 44$	Unilateral $n = 107$; Bilateral $n = 41$	Mean max size: 2 ± 2 cm; TD ⩽ 4 cm $n = 89$; TD > 4 cm $n = 59$	Median 29 months (range, 2–103 months)
Brouquet (2011); Surgery; (Retro- / prospective, $n = 112$); Houston, U.S.	Sex: M/F: 78/34; mean age 55 year ± 11 year	Mean pp 2.3 lesions ± 2.1	Unilateral $n = 78$; Bilateral $n = 34$	Mean size 1.5 cm ± 1.2	Median 49 months (range, 0.1–159.0 months)
Koga (2006); Surgery; (Retrospective, $n = 58$); Tokyo, Japan	Sex: M/F: 30/28; median age 63 year (range, 33–87 year)	1 lesion $n = 23$; 2 lesions $n = 16$; 3 lesions $n = 10$; 4–12 lesions $n = 9$	Unilateral $n = 45$; Bilateral $n = 13$	TD ⩽ 3 cm $n = 31$; TD > 3 cm $n = 27$	Median 24 months (range, 5–233 months)
Ogata (2005); Surgery; (Retrospective, $n = 76$); Fukuoka, Japan	Sex: M/F: 39/37; mean age 62.9 year (range, 41–83 year)	1 lesion $n = 56$; 2 lesions $n = 15$; 3 lesions $n = 4$; 4 lesions $n = 1$	Unilateral $n = 69$; Bilateral $n = 7$	Mean size 2.69 ± 1.47 (range, 0.7–10.0 cm); TD < 3 cm $n = 29$; TD ⩾ 3 cm $n = 47$	Median 47 months (range, 2–204 months)
Kanemitsu (2010); Surgery; (Prospective); Nagoya, Japan	Sex: M/F: 27/31; median age 62 year (range, 36–84 year)	Median 1 lesion (range, 1–8)	Unilateral $n = 45$; Bilateral $n = 13$	Median max size 2.0 cm (range 1–8 cm)	Median: 39 months (range, 5–94 months) (total group); median 51 months (range, 29–89 months) (surviving patients)
Park (2010); Surgery; (Retrospective, $n = 195$); Seoul, South Korea	Sex: M/F: 122/73; median age 58 year ± 9.5 year	1 lesion $n = 112$; 2–4 lesions I = 70; >5 lesions $n = 10$; unknown $n = 3$	Unilateral $n = 146$; Bilateral $n = 48$	Max size:⩽4 cm $n = 170$; >4 cm $n = 17$; undocumented $n = 8$	Median 42.3 months; loss-to follow-up $n = 1$
Headrick (2001); Surgery; (Retrospective, $n = 58$); Rochester, U.S.	Sex: M/F: 37/21; median age 59 year (range, 31–82 year)	1 lesions $n = 31$; 2 lesions $n = 13$; 3 lesions $n = 10$; 4 lesions $n = 4$	N/A	N/A	Median 62 months (range, 6–201 months)
Hornbech (2011); Surgery; (Retrospective, $n = 53$); Copenhagen, Denmark	N/A		Unilateral $n = 41$; Bilateral $n = 12$	N/A	Mean for all tumor sites; 61.6 months. Only analysis with patients with minimal FU of 36 months
Inoue (2004); Surgery; (Retrospective, $n = 128$); Osaka, Japan	Sex: M/F: 85/43; mean age 61.8 year (range, 39–78 year)	1 lesion $n = 95$; ⩾2 lesions $n = 33$	N/A	N/A	Mean 85.9 months; loss-to follow-up $n = 7$
Chen (2009); Surgery; (Retrospective, $n = 84$); Kyoto, Japan	Sex: M/F: 54/30; median age 65 year (range, 41–86 year)	1 lesion $n = 22$; 2–4 lesions $n = 51$; ⩾5 lesions $n = 11$	Unilateral $n = 68$; Bilateral $n = 16$	TD < 3 cm $n = 18$; TD ⩾ 3 cm $n = 66$	Median 28 months (range, 3–135 months)
Hwang (2010); Surgery; (Prospective, $n = 125$); Gyeonggi-do, South Korea	Sex: M/F: 75/50; median age 60 year (range, 32–80 year); ⩽60 $n = 64$; >60 $n = 61$	1 lesion $n = 77$; ⩽3 lesions $n = 109$; >3 lesions $n = 16$	Unilateral $n = 94$; Bilateral $n = 31$	Median size 1.8 cm (range, 0.5–7.0 cm); TD ⩽ 2 cm $n = 85$; TD > 2 cm $n = 40$	Median 46 months (range, 21–99 months)
Riquet (2010); Surgery; (Retrospective, $n = 117$); Paris, France	Sex: M/F: 74/53; median age 65 year (range, 36–85 year); <65 year $n = 62$; >65 year $n = 65$	Total 314; 1 lesion $n = 75$; ⩾2 lesions $n = 42$	N/A	Median size 3.0 ± 1.9 cm (range, 0.2–9.0 cm); TD < 2.9 cm $n = 64$; TD > 3.0 cm $n = 53$	Median 46 months (range, 2–256 months)
Rama (2008); Surgery; (Retrospective, $n = 62$); Lisbon, Portugal	Sex: M/F: 42/19; mean age 61 year ± 14 year (range, 30–80 year)	Mean 1.6 lesions ± 0.8; 1 lesion: $n = 37$; 2 lesions $n = 13$; ⩾3 lesions $n = 11$	Unilateral $n = 59$; Bilateral $n = 2$	TD ⩽ 3 cm $n = 44$; TD > 3 cm $n = 17$	Mean 39 months ± 39 months (range, 4–173 months); complete $n = 56$, $n = 5$ excluded from analysis
Takakura (2009); Surgery; (Retrospective, $n = 56$); Hiroshima, Japan	Sex: M/F: 26/30; median age 64 year (range 42–76 year)	1 lesion $n = 37$; ⩾2 lesions $n = 19$ (range 2–14)	Unilateral $n = 44$; Bilateral $n = 12$	Median size 2 cm (range 0.5–8.8 cm)	Mean 30 months
Lin (2009); Surgery; (Prospective, $n = 63$); Taipei, Taiwan	Sex: M/F: 39/24; median age 58.7 year (range 32–	1 lesion $n = 41$; 2 lesions $n = 14$; 3 lesions $n = 5$; ⩾4 lesions $n = 3$	Unilateral $n = 51$; Bilateral $n = 12$	Mean size 2.77 cm (range 0.5–8.6 cm); TD < 3 cm $n = 40$;	Median 37.3 months (range, 12–122 months)

Table 2 (*continued*)

Study	Patient sex/age	No. of tumors	Involved lobes	Tumor diameter	Follow-up
	78 year)>60 year n = 29			TD ⩾ 3 cm n = 23	
Zabaleta (2011); Surgery; (Retrospective, n = 84); San Sebastian, Spain	Sex: M/F: 60/24; median age 65.5 year; mean age 65.4 year	1 lesion n = 65; ⩾2 lesions n = 19	N/A	TD > 2 cm n = 48; TD < 2 cm n = 36	Median 43 months (range, 0–130 months)
Pfannschmidt (2003); Surgery; (Retrospective, n = 167); Heidelberg, Germany	Sex: M/F: 103/64; mean age 60.2 year (range, 25–81 year)	Median 1 lesion (range, 1–35); 1 lesion n = 84; ⩾2 lesions n = 83	N/A	N/A	Mean 58.6 ± 42.7 months (range, 0.5–183.9 months)
Higashiyama (2003); Surgery; (Retrospective, n = 100); Osaka, Japan	Sex: M/F: 61/39; mean age 60.3 year (range, 39–79 year); <61 n = 49; ⩾61 n = 51	On radiography: 1 lesion n = 49; 2 lesions n = 25; 3 lesions n = 18; 4 lesions n = 4; 5 lesions n = 1; 6 lesions n = 3: Perioperative: 1 lesion n = 55; 2 lesions n = 23; 3 lesions n = 14; 4 lesions n = 3; 5 lesions n = 2; 6 lesions n = 3	Unilateral n = 79; Bilateral n = 21	Max size 0.2–11.0 cm; TD ⩽ 3 n = 59; TD > 3 n = 41	Median 30.3 months (range, 3.6–168.7 months)
Nakajima (2007); Surgery; (Retrospective, n = 143); Tokyo, Japan	Open: sex: M/F: 49/22; age 59.8 year ± 9.9; Thoracoscopy: M/F: 43/29; age 63.3 year ± 11.0	Open 3.4 lesions ± 4.5; scopy 1.6 lesions ± 0.9	N/A	Max TD: open 2.7 cm ± 1.8; scopy 1.5 cm ± 0.9	46.7 months ± 54.3 months (open group); 34.4 months ± 22.0 months (thoracoscopy group)
Shiono (2004); Surgery; (…-spective, n = 87); Tokyo, Japan	Sex M/F: 57/30; median age 61 year (range, 23–83 year)	1 lesion n = 66; 2 lesions n = 9; 3 lesions n = 8; 4 lesions n = 3; 5 lesions n = 1	N/A	Median size 1.8 cm (range 0.7–6.7 cm); TD ⩽ 3 cm n = 66; TD > 3 cm n = 21	Median 32 months (range, 1–110 months)
Sakamoto (2010); Surgery; (Retrospective, n = 59); Tokyo, Japan	Total group: M/F: 162/81, median age 66 year (range, 9–86 year); Metastasis group M/F: 81/52, median age 63 year (range 9–82 year)	N/A	N/A	Total group: median size 1.5 cm (range 0.2–9.5 cm); metastasis group median size 1.5 cm (range 0.2–7.5 cm); Metastasis group TD < 3 cm n = 117; TD ⩾ 3 cm n = 16	Median: 37 months (range, 0–132 months) (for both total group and metastasis group)
Kanzaki (2011); Surgery; (Retrospective, n = 156); Osaka, Japan	Sex: M/F: 91/65; mean age 62 year (range, 39–83 year)	1 lesion n = 100; 2 lesions n = 32; ⩾3 lesions n = 24	Unilateral n = 130; Bilateral n = 26	Max TD ⩽ 3 cm n = 115; TD > 3 cm n = 41	Median 43 months (range, 4–270 months)
Rolle (2006); Surgery; (…-spective, n = 91); Dresden, Germany	Sex: M/F: 164/164; mean age 61 year (range, 20–80 year)	Total 3267 nodules (average 10/pt); 1 lesion n = 92; ⩾4 lesions n = 161; ⩾10 lesions n = 69; ⩾20 lesions n = 30	Unilateral n = 165; Bilateral n = 113	Range of TD 0.3–8 cm	N/A
Rolle (2006); Surgery; (…-spective, n = 91); Dresden, Germany	Sex: M/F: 164/164; mean age 61 year (range, 20–80 year)	Total 3267 nodules (average 10/pt); 1 lesion n = 92; ⩾4 lesions n = 161; ⩾10 lesions n = 69; ⩾20 lesions n = 30	Unilateral n = 177; Bilateral n = 151	N/A	Mean 31 months, median 22.5 months (range, 1–198 months)

pp = per patient.
TD = Tumor Diameter.

Local control

All treatment outcome data are summarized in Table 3.

Local control of treated metastases differed between the studies. Data on local control were not always provided but if so, these data were reported in either progression free survival (PFS) or disease free survival (DFS). Median PFS reported in the RFA studies by Yan et al.[13,14] was 15 months (range, 3–40), while 2-year local PFS was 56%.[14] Data on local control were not provided in other RFA studies.

Six surgery studies reported local control. Brouquet et al.[18] and Ogata et al.[20] provided DFS data for patients treated with both hepatic and pulmonary metastasectomy, with 5-year DFS being 25% and 27% respectively. Ogata et al.[20] also reported on data on 5-year lung DFS being 35%.

The 5-year DFS reported by Chen et al.[21] and Lin et al.[22] were 34.4% and 19.5%, respectively. Rama et al.[19], reported a mean DFS of 52 months ± 6 months and Takakura et al.[23] found a DFS of 13 months (range, 2–35 months).

Overall survival

Median Overall Survival (OS) was reported in 11 of 27 articles. For RFA, Yamakado et al.[12] reported a median OS of 38 months. The two articles by Yan et al.[13,14] reported from the one dataset of 55 patients and provided a median OS of 33 months (range, 4–40 months). The fourth study concerning RFA by Chua et al.[15] reported a median OS of 51 months (95% CI, 19–83 months) for the total study population of 148 patients with pulmonary metastases from several primary tumors. Outcome data for the colorectal cancer patient subgroup were not available.

Regarding surgery, in the study of Brouquet et al.[18], the median OS was 58 months for patients with both liver and lung metastasectomy. Retrospective studies by Koga et al.[24] and Hornbech et al.[25] reported median OS of 27 months and 33.5 months, respectively. Hornbech et al.[25] also analyzed the median survival of subgroups with (15.4 months) or without (28.6 months) concurrent hepatic metastases. Hwang et al.[26] conducted a prospective study with a median OS of 37 months whereas the retrospective studies by Zabaleta et al.[27] and Pfannschmidt et al.[17] reported median OS of 72 months (range, 0–129 months) and 40.2 months, respectively.

One study (Rama et al.[19]) reported only a mean OS of 67 months ± 16 months.

Survival rates

Good comparison between survival rates was difficult since these outcome data were differently reported between the papers.

Table 3
Treatment outcome.

Study	Number of patients (n)	Retro- (R) or prospective (P)	Treatment outcome
Yamakado (2009)	78	R	SR 1-year/3-year/5-year: 83.9%/56.1%/34.9%; Median Survival 38.0 months
Yan (2006)	55	R	PFS median 15 months (range, 3–40 months); SR 1-year/2-year/3-year: 85%/64%/46%; Median OS 33 months (range, 4–40 months)
Yan (2007)	55	R	PFS median 15 months (range, 3–40 months); Local PFS 1-year/2-year: 74%/56%; SR 1-year/2-year/3-year: 85%/64%/46%; Median OS 33 months (range, 4–40 months)
Chua (2010)	108	R	PFS median 11 months (95% CI, 9–14 months); SR 3-year/5-year: 60%/45%; median OS 51 months (95% CI, 19–83 months)
Brouquet (2011)	112	P	DFS 3-year/5-year: 28%/25% (both liver and lung metastasis) SR 3-year/5-year: 71%/50%; median 58 months (after liver + lung resection
Koga (2006)	58	R	SR 5-year/10-year: 29%/20% median survival time 27 months
Ogata (2005)	76	R	DFS 5-year cumul. 27%; lung DFS 5-year cumul. 35%; Cumul. SR 5-year 32% (after first resection)
Kanemitsu (2010)		P	SR 1-year/2-year/3-year/5-year: 96.6%/84.5%/70.5%/48.9%
Park (2010)	195	R	SR 5-year: 71.2%
Headrick (2001)	58	R	SR 5-year/10-year: 30%/16%
Hornbech (2011)	53	R	Estimated SR 5-year: 50.3%, median 33.5 months (total group); 0%, median 15.4 months (also hepatic M+); 61.7%, median 28.6 months (no-hepatic M+)
Inoue (2004)	128	R	Estimated SR 5-year: 45.3%
Chen (2009)	84	R	DFS 5-year/10-year: 34.4%/30.6%; SR 5-year/10-year: 60.5%/48.4%
Hwang (2010)	125	P	Median 37 months
Riquet (2010)	117	R	SR 5-year/10-year: 41%/27%, median 45 months
Rama (2008)	62	R	DFS mean 52 ± 6 months; SR 3-year/5-year/10-year: 61%/48%/11%, mean 67 ± 16 months
Takakura (2009)	56	R	DFS 13 months (range, 2–35 months); cumul. SR 3-year/5-year 64.9%/48.2%
Lin (2009)	63	P	DFS 5-year: 19.5%; SR 5-year/10-year: 43.9%/19.5%
Zabaleta (2011)	84	R	SR 3-year/5-year: 70.2%/54.3%, median 72 months (range, 0–129 months)
Pfannschmidt (2003)	167	R	Cumul. SR 5-year: 32.4%, median 40.2 months
Higashiyama (2003)	100	R	SR 3-year/5-year: 62.2%/49.4%
Nakajima (2007)	143	R	SR 5-year: 49.3% (open resection group), 39.5% (thoracoscopy group)
Shiono (2004)	87	R	SR 5-year: 61.4%
Sakamoto (2010)	59	R	SR 5-year: 69.9% (CRC patients)
Kanzaki (2011)	156	R	SR 3-year/5-year/10-year: 71.4%/56.2%/44%
Rolle (2006)	91	R	SR 5-year: 41% (complete resection); 7% (incomplete resection)
Rolle (2006)	91	R	SR: 1-year/3-year/5-year: 81%/53%/35% (all 328 patients) 85%/59%/41% (complete resection) 60%/23%/7% (incomplete resection)

For a summary of the survival rates provided in the articles, see Table 3. For analysis 2- and 5-year survival rates were chosen, since these were the two most reported survival data. In papers which did not provide either of these, but did have a Kaplan–Meier curve, 2- and 5-year survival rates were extracted manually from this curve.

For RFA 2-year survival rate (SR) ranged from 64–73%[12–15] and 5-year SR from 34.9–45%.[12,15] The surgical series provided 2-year SR range from 64–88%.[17–25,28–32] The 5-year SR reported for surgery ranged from 29–71.2%.[17–25,27–35] As seen in various uni- and multivariate analyses[12–14,35], survival outcomes are influenced by the size of the intrapulmonary lesion, especially in patients treated with RFA. Tumors larger than 3 cm give significantly shorter long-term survival and local control rates than lesions smaller than 3 cm.

Mean and median tumor size were difficult to compare between surgery and RFA studies, due to differences in reporting, but seemed similar for both therapies (Table 2).

Complications

In only 20 articles treatment-related mortality and/or morbidity were described, which are tabulated (Table 4). The remaining 7 studies were not included in this table.

Treatment-related mortality rates were reported by three of the studies investigating RFA.[13–15] Mortality rate was 0% in all three, but was defined differently (Table 4). Morbidity and complication rates differed but all four RFA studies reported pneumothorax as the most common post-treatment complication (22% of sessions[12], 29% of patients[13,14] and 45% of patients[15]).

Three surgical studies reported treatment-related mortalities (Zabaleta et al.[27], Pfannschmidt et al.[17], Nakajima et al.[36]) of 2.4%, 1.8% and 1.4%, respectively. All other fourteen studies which reported complications showed mortality rates of 0%.[13–15,18–20,24,26,28,31–35,37,38]

Morbidity rates ranged from 0–14.5%, with large variations in the reporting of complications. Some studies for example reported only major morbidity (e.g. Kanzaki et al.[32]) whereas others reported all complications that occurred.

Discussion

Since the proposal of the existence of oligo-metastases by Hellmann et al.,[3] local therapies have been used for treating these few distant metastases with curative intent. For oligo-metastases in the lung, the most commonly used local treatment modalities are surgery, RFA and SBRT, see Fig. 2. To our knowledge the present study was the first to systematically review and try to compare metastasectomy, RFA and SBRT for patients with pulmonary metastases of colorectal cancer with regard to local tumor control, OS and complications.

By systematically searching databases, we identified 27 published studies, of which four were dealing with RFA and 23 with surgery.[12–38] No eligible studies were found on SBRT, even after adjusting the selection criteria to a minimum of 25 patients and a minimal follow-up of 12 months. For this reason, no analysis was made on SBRT data. Of the included four RFA series, three studies were from the same institute, which has to be kept in mind given the possibility that some patient data may be used in multiple studies and therefore may bias outcome data. In two surgical

Table 4
Complications.

Study	Mortality rate	Morbidity rate	Complications
Yamakado (2009)	N/A	N/A	Pneumothorax in 31/140 sessions (22.1%), chest tube placement in 18 sessions; aseptic pleuritis with chest tube placement in 2 sessions (1.4%); Minor complication 13/140 (9.3%); Major complication 20/140 (14.3%)
Yan (2006)	0%	42%	Post-RFA: pneumothorax (16), fever (6), pleural effusion (4), pleuritic chest pain (2); chest drain n = 10, nine for pneumothorax, 1 for pleural effusion. Duration of chest drain 2 ± 2 days
Yan (2007)	0%	42%	Intrapulmonary bleeding (5); pneumothorax (16); pleural effusion (4); persistent pleuritic chest pain more than 1 week (2)
Chua (2010)	0%	N/A	Morbidity: pneumothorax (66), pleural effusion (16), consolidation (10), bleeding (1), pleuritic chest pain (12); chest tube placement (45) of which one ptn developed severe consolidation and lung abcess with empyema
Brouquet (2011)	0%	4%	For lung resection only: Mortality 0% (Treatment-related); Morbidity 4% (n = 4) (postoperative)
Koga (2006)	0%	N/A	N/A
Ogata (2005)	0%	1%	Hemorrhage n = 1
Park (2010)	0%	N/A	N/A
Headrick (2001)	0%	12%	Ileus (2), bile leak (1), chyle leak (1), incisional hernia (1), postoperative bleeding (1), pulmonary embolus (1)
Hwang (2010)	0%	N/A	N/A
Riquet (2010)	0%	14.5%	Atrial fibrillation (2); persistent air leaks (6); atelectasis (1); empyema (2); hemorrhage (2); pneumonia (1); recurrent nerve palsy (1); miscellaneous (2)
Rama (2008)	0%	8%	Bronchopleural fistulae (2); acute renal insufficiency (1), hemorrhage (1); wound infection (1)
Zabaleta (2011)	2.4% (n = 2)	8.3%	Persistent air leaks (3); nosocomial pneuomonia (1); partial intestinal obstruction (1); atelectasis (1) requiring bronchoscopy, haematothorax (1) (requiring reintervention)
Pfannschmidt (2003)	1.8% (n = 3)	N/A	Postoperative deaths by septic multiorgan failure after pneumonia (2); death by sudden cardiac failure (1)
Nakajima (2007)	1.4%	N/A	Postoperative deaths (pulmonary thromboembolism; gastrointestinal bleeding) (2)
Shiono (2004)	0%	N/A	N/A
Sakamoto (2010)	0%	9.8%	Persistent air leak (3); pneumonia (2); cerebral infarction, postoperative bleeding, atelectasis, duodenal ulcer, chylothorax, ileus, urinary tract infection, empyema (1 each)
Kanzaki (2011)	0%	0%	N/A
Rolle (2006)	0%	N/A	Major morbidity: persistent air leaks (2); intrapleural bleeding (2); late pneumothorax (2)
Rolle (2006)	0%	N/A	Major morbidity: persistent air leaks (2); intrapleural bleeding (2); late pneumothorax (2)

Perioperative; In-hospital; Treatment-related; Operative; Postoperative; 30-day.
Including hepatic surgery complications.
Metastasis group.

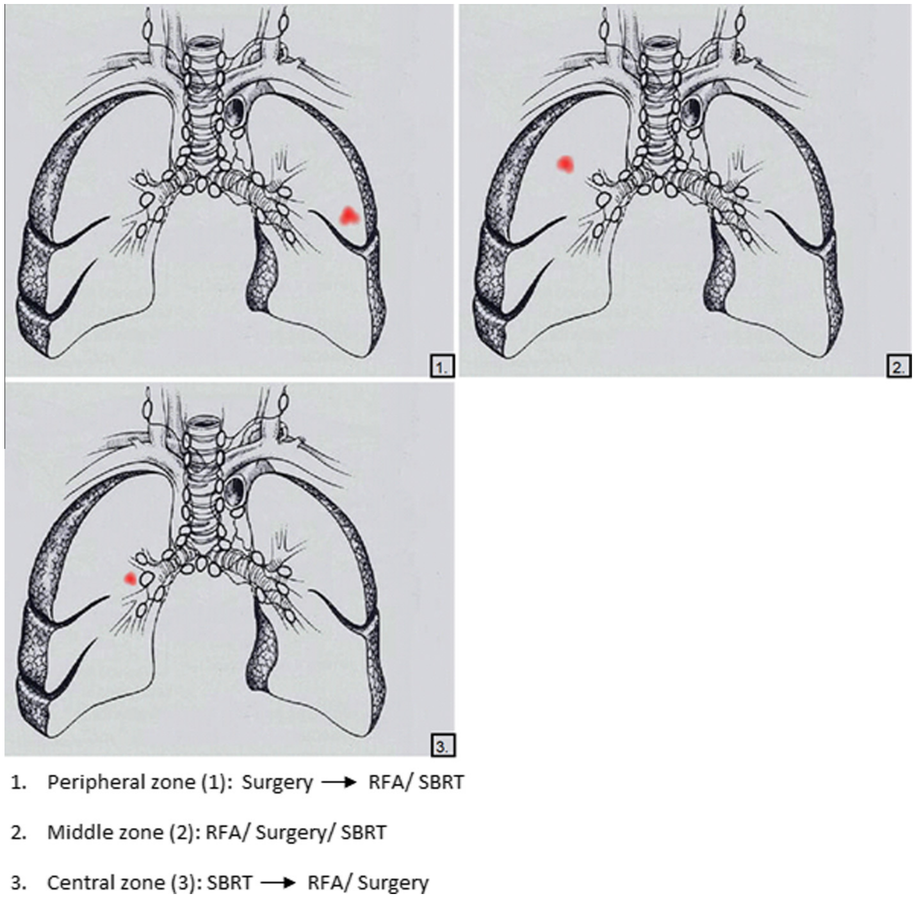

Fig. 2. Leuven–Maastricht guideline map for the local treatment of lung metastases.

series, the same patient population is used, which was the reason to use these data only once in our analysis.

In the identified papers, outcome data were reported in various ways, with different parameters mentioned or sometimes incomplete data. This resulted in difficulties analyzing and comparing these outcomes. Also, diagnostic differences may have influenced outcome, such as differences in CT slice thickness. This is not always reported clearly but could influence outcome results. Survival outcomes used for analysis are either reported in the papers or extracted manually from Kaplan–Meier curves and weighted for number of patients afterwards. Since there is a strong heterogeneity in the reporting of outcome data, the quality op comparisons between surgery and RFA are difficult en should be approached with care. Comparing RFA and surgery, the differences in OS are small and in the absence of randomized trial, no firm conclusions can be drawn. Since tumors larger than 3 cm give significantly shorter long-term survival and local control rates than lesions smaller than 3 cm, differences in tumor size in the included patients in the RFA and surgery studies may have influenced the results.

Investigating complication rates, RFA seems to have better outcomes, since the mortality rate in 3 studies was 0%, compared to mortality rates of 1.4–2.4%, reported in three surgical studies.[17,27,32] However, morbidity rates are higher in the RFA studies compared with the surgery papers, with an average of 45.5% for the three studies[12–15] compared with 6.6% in nine surgical studies[18–20,27,28,32,34,35,37] (Table 4). The problem however, is that probably not all complications are reported, mainly in these surgery articles, in which sometimes only major complications are reported.

Because of the wide variety in data, caused by patient selection and the lack of phase III trials, no conclusions can be drawn on effectiveness of surgery for lung metastases of colorectal cancer in comparison to RFA.

This review points out that there is a need for prospective, randomized studies, including studies that investigate the effectiveness and long-term survival of SBRT and RFA. It is to our opinion very likely that SBRT represents an effective treatment method in this population. Based on outcomes from studies investigating SBRT for primary lung cancer, e.g. Timmerman et al.[39], Senan et al.[40] and a review by Fernando et al.[9] in which SBRT and RFA seemed to be effective and useful treatment modalities for high-risk primary lung cancer patients, we assume that outcomes for pulmonary metastases may be comparable to those for primary lung cancer. This assumption is confirmed by the prospective, multicentre study of Lencioni et al.[41] in which both NSCLC and pulmonary metastasized colorectal cancer patients were treated with RFA. This paper was not included in this review because of a follow-up of only 15 months. However, results show that there is no difference in response between these two patient-groups. Overall survival at 1 and 2 years were 70% and 48% respectively for NSCLC and 89% and 66% for patients with colorectal metastases.

Conclusions

Because of the lack of randomized trials, no firm conclusions can be drawn about the relative merits of surgery, RFA and SBRT for colorectal lung metastases. However, only surgical series provide large prospective series with large patient numbers.

Therefore, surgery is the treatment of choice in this condition. Other therapy options such as RFA and SBRT have been reported to be successful as well, but most series are at present too small, retrospective and or have a follow-up that is too short to draw definitive conclusions. Nevertheless, retrospective RFA studies support its effectiveness and this modality may thus be regarded as a less defined alternative for surgery. Finally, because of our stringent a priori inclusion criteria for published series, we could not include radiotherapy studies in this review. Indeed, published studies of SBRT for colo-rectal metastases have still a short follow-up, which is not surprising in view of the relative new technology that SBRT is and its only recent wide-spread use. Assuming an analogous efficacy for colo-rectal metastases as for primary NSCLC, SBRT series when more maturated may well establish radiotherapy as the third local treatment option for patients with colo-rectal lung metastases. Ideally, randomised trials should be performed to define the value of all three modalities, taking into account patient and disease characteristics.

Conflict of interest

None declared.

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